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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,751	06/20/2003	Randy K. Bledsoe	PU4803US	5089
23347	7590	09/20/2005	EXAMINER	
GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY, MAI B475 FIVE MOORE DR., PO BOX 13398 RESEARCH TRIANGLE PARK, NC 27709-3398			STEADMAN, DAVID J	
		ART UNIT		PAPER NUMBER
				1656

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/600,751	BLEDSOE ET AL.
	Examiner David J. Steadman	Art Unit 1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 30 June 2005.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-112 is/are pending in the application.
 4a) Of the above claim(s) 1-37 and 46-112 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 38-45 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 20 June 2003 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>5/3/04, 3/17/04</u> .	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

Status of the Application

- [1] The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.
- [2] Claims 1-112 are pending in the application.
- [3] Applicants' preliminary amendment to the specification, filed on 6/30/2005, is acknowledged.

Election/Restriction

- [4] Applicants' election with traverse of Group V, claims 38-45, in the response filed on 6/30/2005 is acknowledged.

RESPONSE TO ARGUMENT: Applicants traverse the restriction requirement, arguing that a search of SEQ ID NO:6 and 8 would not require a serious burden on the examiner as the sequences differ by a single amino acid.

Applicants' argument is not found persuasive because, while the sequences may differ by a single amino acid, it is false to assume that a reference that teaches the polypeptide of SEQ ID NO:6 would also teach the sequence of SEQ ID NO:8, particularly as the sequences are not obvious over each other. In order to perform a *complete* search of the claims for the elected invention directed to SEQ ID NO:6 and 8, a separate sequence search is required for each of SEQ ID NO:6 and 8. Thus, a

serious burden is required for the examiner to examine Group V as directed to SEQ ID NO:6 and 8.

- [5] The requirement is still deemed proper and is therefore made FINAL.
- [6] Claims 1-37 and 46-112 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claim to Domestic Priority

- [7] Applicants' claim to domestic priority under 35 U.S.C. § 119(e) to provisional application 60/390,610, filed on 6/21/2002, is acknowledged. Applicants' amendment to the specification filed on 6/30/2005 perfects applicants' claim to priority under 35 U.S.C. § 119(e).

Information Disclosure Statement

- [8] All references cited in the IDSs filed on 5/3/2004 and 3/17/2004 have been considered by the examiner. A copy of each Form PTO-1449 is attached to the instant Office action.
- [9] If the examiner has inadvertently overlooked an IDS that has previously been filed in the instant application, applicants' cooperation is requested in alerting the examiner to this IDS in the response to this Office action.

Specification/Informalities

[10] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (for example, page 76, line 5) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

[11] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: -- Method for Identifying a Glucocorticoid Receptor Modulator Using a Computerized Modeling System--.

[12] When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02. See particularly Figure 17.

Claim Objection(s)

[13] Claims 38 and 40 are objected to because of the recitation of "GR" and "TIF2." Abbreviations, unless otherwise obvious, e.g., "DNA," should not be recited in the claims without at least once reciting the entire phrase for which the abbreviations are used. Appropriate correction is required.

[14] Claim 40 recites “co-activator peptide,” while claim 39, from claim 40 depends, recites “co-activator.” It is suggested that applicants maintain consistency of terms used in the claims by, for example, inserting “peptide” after “coactivator” in claim 39 or, alternatively, deleting the first occurrence of “peptide” from claim 40.

[15] Claim 42 is objected to as reciting non-elected subject matter. It is suggested that applicants remove the non-elected subject matter from the claim.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[16] Claims 38-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 38 (claim(s) 39-45 dependent therefrom) are indefinite in the recitation of “a GR polypeptide complex comprising an expanded binding pocket” as it is unclear as to the meaning of the term. It is noted that the term “expanded binding pocket” is defined in the specification at p. 31 as “an NR ligand binding pocket in which atoms in the protein have shifted so as to increase the volume available to the ligand.” Even in view of this definition, the term is indefinite because it has at least three different interpretations as follows: 1) the GR polypeptide complex has an insertion of amino acids in its binding pocket, thus rendering the binding pocket an “expanded binding

pocket;" 2) the GR polypeptide complex, due to, e.g., ligand binding, has undergone a conformational change to expand the volume of the binding pocket; or 3) the GR polypeptide complex in its unliganded form has an open or "expanded" conformation that is closed upon ligand binding. In view of the plurality of different meanings of the term, it is suggested that applicants clarify the meaning of "a GR polypeptide complex comprising an expanded binding pocket."

[b] Claim 38 (claim(s) 39-45 dependent therefrom) are indefinite in the recitation of "a GR polypeptide complex" as it is unclear as to whether "a GR polypeptide complex" is meant to be interpreted as a GR polypeptide and some other additional moiety or if it is meant to encompass only a GR polypeptide. Claim 38 recites "a GR polypeptide complex" and claim 39 recites "wherein the...complex further comprises a co-activator and fluticasone propionate," suggesting that the "GR polypeptide complex" of claim 38 lacks a co-activator and fluticasone propionate. However, the specification at pp. 22-23 states, "[t]he present invention provides for...a complex comprising a soluble GR LBD bound to fluticasone propionate and a TIF2 co-activator peptide," suggesting that, by "complex," applicants intend for the term to encompass a GR polypeptide bound to fluticasone propionate and a TIF2 co-activator peptide. In the interest of advancing prosecution, the examiner has interpreted "a GR polypeptide complex" as meaning only a GR polypeptide, without an additional moiety. It is suggested that applicants clarify the meaning of the term "GR polypeptide complex."

[c] Claim 43 recites the limitation "the ligand." There is insufficient antecedent basis for this limitation in the claim.

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[d] Claim 44 is confusing in the recitation of "coordinates comprise one of the atomic coordinates shown in Table 2 and a subset of the atomic coordinates shown in Table 2." The claim has two interpretations: 1) the coordinates comprise ONE of the atomic coordinates of Table 2 AND a subset of the atomic coordinates shown in Table 2 or 2) the coordinates comprise the atomic coordinates of Table 2 OR a subset of the atomic coordinates shown in Table 2. In the interest of advancing prosecution, the examiner has interpreted the phrase as meaning the coordinates comprise the atomic coordinates of Table 2 OR a subset of the atomic coordinates shown in Table 2. It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[17] Claims 38-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for identifying a GR modulator using a genus of atomic coordinates of a GR polypeptide complex, optionally wherein the atomic coordinates comprise a subset of the atomic coordinates shown in Table 2.

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of recited atomic coordinates, i.e., the atomic coordinates of Table 2. Other than this single representative species, the specification fails to disclose any other additional representative species of the genus of claimed polypeptides. While MPEP § 2163 acknowledges that in certain situations "one species

adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of polypeptides encompasses species that are widely variant with respect to both structure and function, including (but not limited to) polypeptides having any amino acid sequence and any function. As such, the disclosure of the single representative species of the atomic coordinates of Table 2 is insufficient to be representative of the attributes and features of all species encompassed by the recited genus of atomic coordinates.

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[18] Claims 38-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a potential GR modulator by generating a three-dimensional computer model of a complex of the polypeptide of SEQ ID NO:6 liganded to the peptide of SEQ ID NO:9 and fluticasone propionate, wherein the complex has the atomic coordinates of Table 2 and modeling a ligand that fits spatially into the fluticasone propionate binding pocket, wherein a compound that fits spatially into the fluticasone propionate binding pocket of the model identifies a potential GR modulator, does not reasonably provide enablement for the claimed method. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims are so broad as to encompass the use of the atomic coordinates of any GR polypeptide complex. The claims encompass any GR, and any portion thereof that is unliganded or liganded, and, with respect to liganded

GRs, further including any ligand(s) bound thereto, including ligands that have yet to be isolated. The broad scope of recited atomic coordinates of a GR polypeptide complex. In this case the disclosure is limited to a method of identifying a potential GR modulator by generating a three-dimensional computer model of a complex of the polypeptide of SEQ ID NO:6 liganded to the peptide of SEQ ID NO:9 and fluticasone propionate, wherein the complex has the atomic coordinates of Table 2 and modeling a ligand that fits spatially into the fluticasone propionate binding pocket, wherein a compound that fits spatially into the fluticasone propionate binding pocket of the model identifies a potential GR modulator.

The lack of guidance and working examples: The specification provides only a single working example of the claimed method, the working example using a three dimensional computer model of a complex of the human GR ligand binding domain polypeptide of SEQ ID NO:6 liganded to the peptide of SEQ ID NO:9 and fluticasone propionate, wherein the complex has the atomic coordinates of Table 2. This single working example along with the additional teachings of the disclosure and prior art fail to provide the necessary guidance for making the entire scope of atomic coordinates of a GR polypeptide complex.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The examiner acknowledges that, at the time of the invention, the atomic coordinates of the steroid binding domain of mouse and human GR bound to ligands were known in the art (see Dey et al., Gillner et al., and Apolito et al., all cited in the IDS filed 5/3/2004). However, as acknowledged by applicants, it is highly

unpredictable as to whether these structural coordinates represent all GR protein complexes (specification at p. 9, bottom).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: As noted above, methods for generating three dimensional models of the ligand binding domain of GR were known in the art at the time of the invention. However, it was not routine to *make* all three dimensional models of any GR and any portion thereof bound to any ligand(s), including ligands that have yet to be isolated as encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

[19] Claims 38 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Gillner et al. (WO 00/52050; cited in the IDS filed 5/3/2004). The claims are drawn to a method for identifying a GR modulator using a computerized model of GR. MPEP 2111.01 states that “[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow.” Claim 44 recites, “the atomic coordinates comprise...a subset of the atomic coordinates shown in Table 2.” A *subset* of the atomic coordinates can be any set of atom types, any residues, any values of vector x, y, and/or z of Table 2. Accordingly, the examiner has broadly interpreted “the atomic coordinates comprise...a subset of the atomic coordinates shown in Table 2” in claim 44 as encompassing atomic coordinates of essentially *any* GR polypeptide.

Gillner et al. teaches homology modeling of a human GR ligand binding domain in complex with various steroid ligands (claims 12-13).

This anticipates claims 38 and 44 as written.

[20] Claims 38 and 42-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Apolito et al. (WO 03/015692; cited in the IDS filed 5/3/2004). The teachings of WO 03/015692 stated below were first disclosed in application 60/305,902, to which WO 03/015692 claims priority.

The claims are drawn to a method for identifying a GR modulator using a computerized model of GR and optionally further comprising the step of determining whether the modulator increases or decreases GR polypeptide activity.

Apolito et al. teaches a method for identifying a GR modulator by modeling the structure of the ligand binding domain of a human GR that comprises a sequence that is 100% identical to SEQ ID NO:6 herein (see Appendix A) complexed with a TIF2 ligand and a dexamethosone agonist, and identifying modeled compounds, including non-steroid compounds, that interact with the human GR ligand binding domain and optionally screening the compound for its effect on a GR polypeptide (pp. 14 and 54-66 and claims 82, 84, and 88).

This anticipates claims 38 and 42-45 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

[21] Claim(s) 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apolito et al. in view of Johnson (*Ann Allergy Asthma Immunol* 81:35-40) and Högger et al. (*Steroids* 59:597-602). Claims 39-41 limit the GR polypeptide complex of claim 38 to further comprising a co-activator, optionally TIF2, and fluticasone propionate.

Apolito et al. discloses the teachings as set forth above.

Johnson teaches the structure of fluticasone propionate (p. S435).

Högger et al. teaches fluticasone propionate is clinically superior to other glucocorticoids, including dexamethosone (p. 597, abstract) because it has a higher association constant, a slower dissociation constant, and a significantly lower dissociation constant (p. 599).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Apolito et al., Johnson, and Högger et al. to substitute dexamethosone with fluticasone propionate in practicing the screening method of Apolito et al. (using a model of GR bound to TIF2 and dexamethosone). One would have been motivated to substitute dexamethosone with fluticasone propionate in practicing the screening method of Apolito et al. because fluticasone propionate is a clinically superior agonist of GR and one would have wanted to determine a structural basis for the differences in GR affinity for dexamethosone versus fluticasone propionate in order to design more potent agonist compounds. One would have a reasonable expectation of success for substituting dexamethosone with fluticasone propionate in practicing the screening method of Apolito et al. because of the results of Apolito et al.

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and Johnson. Therefore, claims 39-41, drawn to a the screening method as described above, would have been obvious to one of ordinary skill in the art.

Conclusion

[22] Status of the claims:

Claims 1-112 are pending.

Claims 1-37 and 46-112 are withdrawn from consideration.

Claims 38-45 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

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APPENDIX A

RESULT 4
ABU08023
ID ABU08023 standard; protein; 777 AA.
XX
AC ABU08023;
XX
DT 10-MAY-2003 (first entry)
XX
DE Wild-type human glucocorticoid receptor (GR).
XX
KW Human; receptor; protein coordinate data; glucocorticoid receptor; GR;
KW ligand binding domain; LBD; nuclear receptor; NR; modulator;
KW glucocorticoid; cellular proliferation; GRLBD; TIF2; dexamethasone;
KW GRalpha; androgen receptor; progesterone receptor;
KW mineralocorticoid receptor; GRbeta; inflammation; tissue rejection;
KW autoimmunity; cancer; leukaemia; lymphoma; urticaria; asthma;
KW ulcerative colitis; hepatitis; cirrhosis; inflammatory bowel disease;
KW rheumatoid arthritis; psoriasis; HIV; cell apoptosis; steroid receptor.
XX
OS Homo sapiens.
XX
PN WO2003015692-A2.
XX
PD 27-FEB-2003.
XX
PF 17-JUL-2002; 2002WO-US022648.
XX
PR 17-JUL-2001; 2001US-0305902P.
XX
PA (SMIK) SMITHKLINE BEECHAM CORP.
XX
PI Apolito CJ, Bledsoe RK, Lambert MH, McKee DD, Montana VG;
PI Pearce KH, Stanley TB, Xu HE;
XX
DR WPI; 2003-268235/26.
DR N-PSDB; ABX12865.
XX
PT Novel glucocorticoid receptor ligand binding domain polypeptide in
PT crystalline form, useful for identifying modulator of activity of the
PT polypeptide that are useful for treating inflammation, cerebral edema,
PT asthma.
XX
PS Disclosure; Page 294-297; 347pp; English.
XX
CC The invention discloses a substantially pure glucocorticoid receptor (GR)
CC ligand binding domain (LBD) polypeptide in crystalline form. GR is a
CC nuclear receptor (NR) which can modulate the transcription of DNA. They
CC are receptors for various cellular molecules, including glucocorticoids,
CC which has been associated with cellular proliferation. Also disclosed are
CC methods for generating a crystallised GR LBD polypeptide, screening
CC several compounds for a modulator of a GR LBD polypeptide, modifying a
CC test NR polypeptide, isolating GR polypeptide with a mutation in the LBD,
CC which is a substitution of a hydrophobic amino acid residue by a
CC hydrophilic amino acid residue and specific antibodies. The atomic
CC structure coordinates of GRLBD in complex with TIF2 and dexamethasone is
CC useful for designing a modulator of a NR, for identifying a GR modulator
CC (preferably a modulator that selectively modulates activity of GRalpha
CC polypeptide compared to other GR polypeptides), for identifying a
CC compound that inhibits binding of a ligand to GR polypeptide and for
CC identifying a NR modulator that selectively modulates the biological
CC activity of a NR compared to GRalpha. The NR is androgen receptor,
CC progesterone receptor, mineralocorticoid receptor, GRbeta and its
CC isoforms that have ligands that also bind GRalpha. The mutated GR
CC polypeptides improve the solubility, stability in solution. The antibody

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CC is useful for detecting a level of GR polypeptide in a biological sample.
CC The identified GRalpha LBD polypeptide activity modulators are useful for
CC treating conditions such as inflammation, tissue rejection, autoimmunity,
CC cancer, leukaemia, lymphoma, urticaria, asthma, ulcerative colitis,
CC hepatitis, cirrhosis, inflammatory bowel disease, rheumatoid arthritis,
CC psoriasis, HIV and cell apoptosis. The sequences disclosed are the GR
CC polypeptides and nucleic acids (wild-type and mutant), PCR primers used
CC to amplify/mutate them and similar steroid receptors

XX

SQ Sequence 777 AA;

Query Match 100.0%; Score 1340; DB 6; Length 777;
Best Local Similarity 100.0%; Pred. No. 3.7e-126;
Matches 257; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 VPATLPQLTPLVSLEVIEPEVLYAGYDSSVPDSTWRIMTTLNMLGGRQVIAAVKWAKA 60
||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||

Db 521 VPATLPQLTPLVSLEVIEPEVLYAGYDSSVPDSTWRIMTTLNMLGGRQVIAAVKWAKA 580

Qy 61 IPGFRNLHLDQM TLQYSWMFLMAFALGWR SYRQSSANLLCFAPD LIINEQRMTLPCMY 120
||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||

Db 581 IPGFRNLHLDQM TLQYSWMFLMAFALGWR SYRQSSANLLCFAPD LIINEQRMTLPCMY 640

Qy 121 DQCKHMLYVSS ELHRLQVSYEEYLCMKTLLLSSVPKDGLKSQELFDEIRMTYIKELGKA 180
||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||

Db 641 DQCKHMLYVSS ELHRLQVSYEEYLCMKTLLLSSVPKDGLKSQELFDEIRMTYIKELGKA 700

Qy 181 IVKREGNSSQN WQRFYQLTKLDSMHEV VENLLNYC FQTF LDKTMSIEFPEMLAEIITNQ 240
||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||

Db 701 IVKREGNSSQN WQRFYQLTKLDSMHEV VENLLNYC FQTF LDKTMSIEFPEMLAEIITNQ 760

Qy 241 IPKYSNGNIKKLLFHQK 257
||| ||| ||| ||| ||| |||

Db 761 IPKYSNGNIKKLLFHQK 777

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APPENDIX B

RESULT 10
ABU08031
ID ABU08031 standard; peptide; 25 AA.
XX
AC ABU08031;
XX
DT 10-MAY-2003 (first entry)
XX
DE Nuclear receptor coactivator TIF2.
XX
KW Human; glucocorticoid receptor; GR; ligand binding domain; LBD;
KW nuclear receptor; NR; modulator; glucocorticoid; cellular proliferation;
KW GRLBD; TIF2; dexamethasone; GRalpha; androgen receptor;
KW progesterone receptor; mineralocorticoid receptor; GRbeta; inflammation;
KW tissue rejection; autoimmunity; cancer; leukaemia; lymphoma; urticaria;
KW asthma; ulcerative colitis; hepatitis; cirrhosis;
KW inflammatory bowel disease; rheumatoid arthritis; psoriasis; HIV;
KW cell apoptosis; steroid receptor.
XX
OS Homo sapiens.
XX
PN WO2003015692-A2.
XX
PD 27-FEB-2003.
XX
PF 17-JUL-2002; 2002WO-US022648.
XX
PR 17-JUL-2001; 2001US-0305902P.
XX
PA (SMIK) SMITHKLINE BEECHAM CORP.
XX
PI Apolito CJ, Bledsoe RK, Lambert MH, McKee DD, Montana VG;
PI Pearce KH, Stanley TB, Xu HE;
XX
DR WPI; 2003-268235/26.
XX
PT Novel glucocorticoid receptor ligand binding domain polypeptide in
PT crystalline form, useful for identifying modulator of activity of the
PT polypeptide that are useful for treating inflammation, cerebral edema,
PT asthma.
XX
PS Claim 59; Page 105; 347pp; English.
XX
CC The invention discloses a substantially pure glucocorticoid receptor (GR)
CC ligand binding domain (LBD) polypeptide in crystalline form. GR is a
CC nuclear receptor (NR) which can modulate the transcription of DNA. They
CC are receptors for various cellular molecules, including glucocorticoids,
CC which has been associated with cellular proliferation. Also disclosed are
CC methods for generating a crystallised GR LBD polypeptide, screening
CC several compounds for a modulator of a GR LBD polypeptide, modifying a
CC test NR polypeptide, isolating GR polypeptide with a mutation in the LBD,
CC which is a substitution of a hydrophobic amino acid residue by a
CC hydrophilic amino acid residue and specific antibodies. The atomic
CC structure coordinates of GRLBD in complex with TIF2 and dexamethasone is
CC useful for designing a modulator of a NR, for identifying a GR modulator
CC (preferably a modulator that selectively modulates activity of GRalpha
CC polypeptide compared to other GR polypeptides), for identifying a
CC compound that inhibits binding of a ligand to GR polypeptide and for
CC identifying a NR modulator that selectively modulates the biological
CC activity of a NR compared to GRalpha. The NR is androgen receptor,
CC progesterone receptor, mineralocorticoid receptor, GRbeta and its
CC isoforms that have ligands that also bind GRalpha. The mutated GR
CC polypeptides improve the solubility, stability in solution. The antibody
CC is useful for detecting a level of GR polypeptide in a biological sample.

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CC The identified GRalpha LBD polypeptide activity modulators are useful for
CC treating conditions such as inflammation, tissue rejection, autoimmunity,
CC cancer, leukaemia, lymphoma, urticaria, asthma, ulcerative colitis,
CC hepatitis, cirrhosis, inflammatory bowel disease, rheumatoid arthritis,
CC psoriasis, HIV and cell apoptosis. The sequences disclosed are the GR
CC polypeptides and nucleic acids (wild-type and mutant), PCR primers used
CC to amplify/mutate them and similar steroid receptors
XX

SQ Sequence 25 AA;

Query Match 100.0%; Score 71; DB 6; Length 25;
Best Local Similarity 100.0%; Pred. No. 3.2e-05;
Matches 14; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 KENALLRYLLDKDD 14
|||:|||||:
Db 9 KENALLRYLLDKDD 22